

**EVALUATION OF EFFICACY OF INTRATHECAL SUFENTANIL WITH LOW DOSE
BUPIVACAINE IN LOWER SEGMENT CAESAREAN SECTION**

A study of 80 cases

**DISSERTATION SUBMITTED FOR THE DEGREE OF
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CHENNAI**

**DEPARTMENT OF ANAESTHESIOLOGY
MADURAI MEDICAL COLLEGE
MADURAI**

CERTIFICATE

This is to certify that the dissertation entitled “**EVALUATION OF EFFICACY OF INTRATHECAL SUFENTANIL WITH LOW DOSE BUPIVACAINE IN LOWER SEGMENT CAESAREAN SECTION**” is a bonafide record work done by **Dr.M.VIJAYASANKAR**, in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

Dr. I. CHANDRASEKARAN M.D, D.A.,

Professor and Head,
Department of Anaesthesiology,
Government Rajaji Hospital,
Madurai Medical College, Madurai.

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INTRODUCTION

‘Relief of pain is purchased always at a price’

-Ralph waters

‘For all the happiness mankind can gain is not in pleasure but in rest from pain’

-John Dyrden.

The aim of anaesthesiology as a science is the removal of pain temporarily, started initially with pain relief for surgeries, extending now on to postoperative pain relief, chronic pain and cancer pain.

Spinal anaesthesia plays a major role in alleviating pain intraoperatively extending sometime into postoperative period also.

The entry of Corning’s needle in 1885 into subarachnoid space paved the way for the greatest leap into the spinal anaesthesia. His works “Be the density of this observation, what it may have seemed to me on the whole, worth recording”. This opened the prologue for the work “spinal anaesthesia”.

Cocaine was the drug first used experimentally in dogs. In men the first spinal anaesthesia was conducted by “August Bier” on 16 August 1898 with cocaine 3ml as 0.5% solution followed by Matas in America and Tuffier in France.

Spinal anesthesia for caesarean section has always enjoyed popularity as it eliminates the complication of pulmonary aspiration and avoids the problem of difficult airway observed with general anaesthesia. The other advantages of this technique are its simplicity, rapidity in onset and dependability.

The demonstration of opiate receptors in the substantia gelatinosa of spinal cord (Yaksh and Rudy 1976) has created interest in the intrathecal administration of opiates.

The use of Intrathecal morphine for providing postoperative pain relief in caesarean section was started in the year 1988 by Ezzaz Aboulesish et al.

The advantages of neuraxial opioids over neuraxial local anaesthetics are that, it produces prolonged, intense, selective, segmental analgesia without motor blockade and sympathetic dysfunction.

Opioids and local anesthetics administered together have a potent synergistic analgesic effect. Intrathecal opioids enhance analgesia from sub therapeutic dose of local anaesthetic and make it possible to achieve successful spinal anaesthesia using otherwise inadequate doses of local anaesthetic.

Hence, the present study has been undertaken to combine “sufentanil” a recently introduced opioid in Indian market and “bupivacaine”, a long acting local anaesthetic for intrathecal administration to provide anaesthesia for caesarean section.

AIM OF THE STUDY

1. To evaluate the effect of intrathecal sufentanil in improving the quality of anaesthesia with 0.5% hyperbaric bupivacaine in low dose for lower segment caesarean section.
2. To evaluate the efficacy of intrathecal sufentanil in providing postoperative pain relief for lower segment caesarean section.
3. To assess the duration of pain relief.
4. To assess the incidence of side effects

ANATOMY OF SUBARACHNOID SPACE

The vertebral column consists of 7 cervical, 12 thoracic, 5 lumbar, 5 sacral and 4-5 coccygeal vertebrae. The sacral and Coccygeal vertebrae are fused in adult life.

The vertebral columns has 4 curvatures. Thoracic and sacral are primary curvatures and concave anteriorly. Cervical and lumbar are secondary curvatures and convex anteriorly. When the spine is fully flexed the cervical and lumbar curvatures are obliterated. During pregnancy there will be an exaggerated lumbar lordosis.

There are 31 pairs of spinal nerves, 8 cervical, 12 thoracic, 5 sacral and 1 coccygeal. Subarachnoid space lies between the arachnoid and piamater. It contains cerebrospinal fluid and it communicates with the ventricular system at the base of the brain.

CONTENTS

- a. Spinal nerve roots
- B. Cerebrospinal fluid
- C. Denticulate ligaments
- D. Spongy reticulum fibres connecting the Pia to Arachnoid and
- E. Blood vessels

Applied anatomy

Pregnancy reduces anaesthetic requirements both during regional as well as general anaesthesia.

During spinal / epidural anaesthesia less local anaesthetics are required to produce a given level of blockade.

The reduced anesthetic requirements are due to

1. Mechanical effects of gravid uterus increasing the intra abdominal pressure, causing epidural venous engorgement and a reduction of both the epidural and subarachnoid spaces.

2. Nerve fibres have increased sensitivity to local anaesthetic due to the increase in progesterone level.

Sub arachnoid block means privation of senses not necessarily implying loss of consciousness.

APPLIED ANATOMY OF VERTEBRAL CANAL

Vertebral canal extends from the foramen magnum to the sacral hiatus, it protects the spinal cord.

Vertebral column is formed by 7 – cervical, 12- vertebral, 12 – thoracic, 5-lumbar, 5- sacral and 4-coccygeal vertebrae.

Each vertebra is composed of a ‘body’ separated from the adjacent vertebra by the intervertebral disc and ‘vertebral arch’ formed by pedicles and laminae, which surround and protect the cord laterally and posteriorly.

VERTEBRAL LIGAMENTS BOUNDING THE CANAL

Supraspinous ligament passes longitudinally over the tips of spinous processes from C7 vertebra to the sacrum.

Interspinous ligament- connecting the two adjacent spinous processes together situated deep to the supraspinous ligament.

Ligamentum flavum extends from laminae to laminae and is composed of yellow elastic fibres. Half of the posterior wall is composed of the bony laminae and half by ligamentum flavum. They become progressively thicker from above downwards.

Posterior longitudinal ligament is on posterior surface of bodies of vertebrae.

Anterior longitudinal ligament runs along the front of the vertebral bodies.

There are seven projections from these vertebral or neural arches.

They are

1. Three muscular processes- two transverse and one spinous for the attachment and ligaments, and
2. Four articular processes- two upper and two lower – which in the lumbar region, prevent rotation by allowing limited flexion and extension between contiguous vertebrae.

Vertebral canal formed by these structures, has deficiencies posteriorly in the midline, called inter laminar foramina, which enlarges during flexion thereby aiding the passage of spinal needle. The direction of spinous processes determines the direction of the spinal needle.

SPINAL CORD

It is the direct continuation of medulla oblongata extending from the upper border of atlas to first lumbar vertebra, below which there is leash of nerve roots termed cauda equine. Spinal nerves are 31 pairs totally.

8- Cervical

12- Thoracic

5- Lumbar

5- Sacral

1- Coccygeal

Each of the spinal nerve is composed of anterior and posterior roots uniting at the level of inter vertebral foramina and form a nerve trunk.

Membranes covering the spinal cord from without are dura mater, arachnoid mater and piamater. Dura and arachnoid end at S2 level. Piamater is closely applied to the spinal cord.

Blood supply

Blood supply is from the anterior spinal artery which is a branch of vertebral artery and also by a pair of posterior spinal arteries which arise

from the posterior inferior cerebellar arteries. There is no anastomosis between these arteries.

Venous channels

The spinal veins are arranged into anterior and posterior plexuses which drain into vertebral, lumbar and azygous veins.

Cerebrospinal fluid (CSF)

Cerebrospinal fluid is the ultra filtrate of plasma from choroid plexus of lateral ventricles, with a pH of 7.4.

The amount of cerebrospinal fluid in spinal canal is 75 ml with a pressure of 70-170mm of H₂O) in lateral position.

It contains,

20-40mg% of protein

45-80 mg% of sugar and

0-5 lymphocytes/mm³ normally

An important factor that determines the spread of drug in CSF is the specific gravity of the drug in relation to that of CSF (baricity) whose specific gravity is 1.003-1.009. (Average 1.004). Hyperbaric solution is one which is denser than CSF at 37°C.

PHYSIOLOGY OF SUBARACHNOID BLOCK

Subarachnoid block implies temporary interruption of nerve transmission by injection of drugs into the subarachnoid space. The blockade of nerve fibres occurs in the order of temperature, pain, proprioception and lastly motor fibres.

Factors controlling the extent and duration of block

1. Specific gravity of the solution is the most important
2. Position of the patient during and immediately after injection
3. Site of injection
4. Volume and concentration of the solution: increasing the dose and concentration prolongs the effect.
5. Patient factors like age, height, pregnancy and obesity.

Effects on cardiovascular system

The most important physiological response to spinal anaesthesia involves the cardiovascular system due to the sympathetic denervation. β fibres are more sensitive than A fibres causing a higher sympathetic block (zone of differential blockade) resulting in vasodilatation and a fall in blood pressure especially if a substantial number of thoracic segments are blocked.

Due to Bain bridge reflex, the fall in blood pressure is associated with

bradycardia. Blockade of cardiac sympathetic fibres from T1-T4 is an additional factor that causes bradycardia.

Effects on Respiratory system

Respiration is not depressed normally. High spinal anesthesia can cause paralysis of intercostal muscles, but resting tidal volume, maximum inspiratory volume and negative intrapleural pressure are not much altered. Expiratory muscles are more affected than inspiratory muscles. Hypoxia may accompany hypotension and is corrected by oxygen via face mask.

Metabolic and hormonal effects

Spinal anaesthesia blocks hormonal and metabolic responses to nociceptive stimuli arising from the operative site, thereby minimizing the rise in blood sugar, cortisol, catecholamines, renin and aldosterone release associated with the stress. Postoperative negative nitrogen balance and secretion of antidiuretic hormone are inhibited.

Hepatic and renal effects

The hepatic blood flow decreases and is directly proportional to the decrease in blood pressure. There may be more of hepatic oxygen extraction. Renal blood flow is maintained by auto regulation and does not decrease till mean arterial pressure falls below 50mm of Hg.

Thermoregulation and shivering

Hypothermia results from heat loss to the cold environment due to sympathetic paralysis caused by the subarachnoid block

Genitourinary systems

Sphincters of the urinary bladder are not relaxed, and the tone of ureters is not greatly altered. Penis is often engorged and flaccid due to paralysis of nervi-erigentes (S2, 3). Post spinal retention of urine may be moderately prolonged as L2 and L3 contain small autonomic fibers and their paralysis lasts longer than that of the larger sensory and motor fibers.

Uterine tone is unchanged in pregnancy. In the absence of hypotension, spinal anaesthesia has got no effect on the progress of labor and uterine blood flow.

Gastrointestinal effects

Preganglionic fibres from T5 to L4 are inhibitory to the gut. So in

sympathetic blockade, the small intestine contracts with relaxed sphincters and peristalsis often remains normal. Handling of the viscera causes discomfort and bradycardia, since vagus is not blocked.

PHYSIOLOGICAL CHANGES DURING PREGNANCY

BODY CONSTITUENTS

Blood volume begins to increase in the first trimester and reaches 50% above the non pregnant level in the third trimester. The red blood cell mass also rises steadily but relatively less than the total blood volume with a consequent reduction in hemoglobin concentration despite raised total hemoglobin content.

CARDIOVASCULAR FUNCTION

Cardiac output, myocardial contractility, heart rate and stroke volume are increased. The increase in cardiac output starts in the first trimester. Arteriovenous oxygen content difference is reduced until the final trimester. Systemic vascular resistance is decreased. No change occurs in pulmonary arterial pressure during pregnancy. Blocking the autonomic nervous system may result in dramatic decrease in systemic arterial pressure during pregnancy, suggesting a chronically active sympathetic tone.

RESPIRATORY FUNCTION

Respiratory tract is edematous due to capillary engorgement.

Functional residual capacity is decreased. Although the enlarging uterus causes elevation of diaphragm, total lung capacity and vital capacity remain unchanged due to compensatory increase in the antero-posterior and transverse diameters of chest. The minute volume increases in late pregnancy due to increase in tidal volume and respiratory rate with an increase in oxygen consumption.

Average changes from non pregnant value

Minute ventilation	+50 %
Tidal volume	+40 %
Breathing rate	-10
PaO ₂	+10 mm of Hg
PaCO ₂	-10 mm of Hg
pH	No change
Total lung capacity	No change
Vital capacity	No change
FRC	-20%
Expiratory reserve volume	-20%
Residual volume	-20%

Airway resistance	-35%
Oxygen consumption	+20%
BMR	+15 – 20 %

RENAL FUNCTION

Changes in renal function are mainly due to increased levels of ACTH, ADH, aldosterone, cortisol and thyroid hormone. Glomerular filtration rate starts increasing early and remains at about 40% above the non pregnant level by midpregnancy. Renal plasma flow also increases as much as 50% and peaks by the end of the second trimester, remaining high until term.

GASTRO INTESTINAL FUNCTION

Gastro intestinal motility decreases due to a direct effect of progesterone and also by an inhibitory effect of progesterone on plasma motilin. The lower esophageal sphincter tone is diminished.

HEPATIC FUNCTION

There are no gross morphological changes but functional changes are present in the liver. The plasma cholinesterase level is decreased

significantly as early as the first trimester and remains low until delivery.

COAGULATION AND FIBRINOLYTIC FUNCTIONS

Plasma levels of factors VII, X, XII and fibrinogen increase during pregnancy, leading to a hypercoagulable state.

EVALUATION OF THE NEONATE

The importance of assessment of the neonate immediately after the birth is to promptly identify the depressed infants, who require active resuscitation. As a guide to identify and to treat the depressed neonate, Apgar score is used.

APGAR SCORE

Virginia Apgar of New York City described a system whereby the condition of a neonate can be assessed at one minute and five minutes after delivery. The Apgar score has been shown to correlate well with acid-base measurements performed immediately after birth.

SL.I. NO	SIGNS	SCORES		
		0	1	2
1	HEART RATE	Absent	<100 / min	>100 / min
2	RESPIRATORY EFFORT	Absent	Slow, irregular	Crying
3	REFLEX IRRITABILITY	No response	Grimace	Crying
4	MUSCLE TONE	Limp	Hypotonia	Active

5	COLOR	Pale; cyanotic	Body pink, extremities cyanotic	Pink
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TIME FOR SUSTAINED RESPIRATION

The time interval between delivery and the establishment of sustained respiration has been used to identify the depressed neonate. A time for sustained respiration greater than 90 seconds indicates a depressed neonate and correlates with Apgar score of 6 or less.

NEUROBEHAVIOURAL TESTING

Neurobehavioral testing is able to detect subtle or delayed effects of drugs administered during labour and delivery that are not appreciated by Apgar score. The testing evaluates neonate's state of wakefulness, reflex (moro, rooting and sucking reflexes) response, muscle tone and response to sound.

PHARMACOLOGY OF DRUGS

PHARMACOLOGY OF BUPIVACAINE

Bupivacaine is an amide linked local anesthetic. It is a hydrochloride salt of d (1)-1butyl 2' 6' pipecoloxylidide and is presented as a racemic mixture.

- It was synthesized by BO af Ekenstem.
- A first report of its use was published in 1963 by Telivuo.
- It is derived from mepivacaine and is a very stable compound and may be autoclaved repeatedly.
- pKa is 8.2. Heptane/ buffer partition co-efficient is 27.5
- Molecular weight is 288. Protein binding is 96%

AVAILABILITY

Ampoules: 0.5% bupivacaine hydrochloride 4ml

0.5% bupivacaine hydrochloride with dextrose (heavy) 4ml

Vials : 0.25%, 0.5% bupivacaine hydrochloride 20ml

DOSAGE

Maximal dose: 3mg/Kg body weight

Uses:

Spinal

Epidural

Caudal

Continuous epidural

Peripheral nerve block

ONSET TIME AND DURATION OF ACTION

SITE OF ACTION	ONSET(minutes)	DURATION (minutes)
INTRATHECAL	5	180-240
EPIDURAL	15-20	165-225
NERVE BLOCKS e.g., Brachial plexus block	15-20	600

PHARMACOKINETICS

Once injected intrathecally, it gets absorbed by the nerve rootlets and results in the desired effect. It is rapidly absorbed from the site of injection, but the rate of absorption depends on the vascularity at the site and presence of vasoconstrictors.

High lipid solubility of bupivacaine makes it easy for nerve and vascular tissue penetration.

80-95% of the absorbed bupivacaine binds to the plasma protein.

DISTRIBUTION

Rapid distribution phase (α)

In this phase the drug is distributed to highly vascular region, $t_{1/2}$ (α) being 2.7 minutes.

Slow disappearance phase (β)

In this phase the drug is distributed to equilibrating tissues, $t_{1/2}$ (β) being 28 minutes.

Biotransformation and excretion phase (δ)

$t_{1/2}$ (δ) being 3.5 hours, clearance is 0.47 litre/minute.

Biotransformation

It is by the liver. The N-dealkylated metabolite is pipecolyloxyline.

Excretion

It is through the kidneys. 4-10% of the drug is excreted unchanged in urine.

Mode of action

(a).Site of action

1. The Spinal nerve rootlet- fine nerve filaments having a large surface area are exposed to the local anaesthetic.
2. The posterior and lateral aspects of the spinal cord itself.

(b).Sodium channel blockade

They impede sodium ion access to the axon-interior by occluding transmembrane sodium channels thus denying the process of polarization and the axon remains polarized. It is a non- depolarization blockade.

PHARMACODYNAMICS

It has got a longer duration of action but a slower onset.

Cardiovascular system

It reduces cardiac output by reducing the sympathetic tone, by slowing the heart rate and by reducing the venous return.

It produces a fall in arterial blood pressure but it is relatively slow and is seldom very profound.

It produces a fall in central venous pressure

It causes an increase in lower limb blood flow

It causes a reduction in incidence of deep vein thrombosis

Respiratory system

Spinal blockade seldom, if ever, causes respiratory problems.

Gastrointestinal tract

There is increase in gastro intestinal motility and emptying of gastric contents is better.

Toxicity

Toxicity is related to plasma level of unbound drug and more likely due to an inadvertent intravenous injection. Systemic toxicity – reactions primarily involve the central nervous system and the cardiovascular system. The blood level required to produce central nervous system toxicity is less than that required to produce circulatory collapse.

Central nervous system toxicity

Initial symptoms include feeling of light headedness and dizziness, followed by visual and auditory disturbances. Objective signs are excitatory and include muscle twitching and tremors. Ultimately generalized tonic, clonic seizures occur.

Cardiovascular system toxicity

The rate of depolarization in fast conduction tissue of purkinjee fibres and ventricular muscle is decreased. The rate of recovery of bupivacaine induced block is slower than that of lignocaine. Extremely high concentration of the drug causes sinus bradycardia and cardiac arrest.

R enantiomer is more toxic than S enantiomer

PHARMACOLOGY OF SUFENTANIL

Sufentanil is a thienyl analogue of fentanyl. The analgesic potency of sufentanil is 5 to 10 times of fentanyl which parallels the greater affinity of sufentanil for opioid receptors compared with that of fentanyl.

It is a synthetic narcotic agonist.

Availability

Available in 1ml, 2ml, 5ml glass vials. Each ml contains 50 micrograms of sufentanil

Routes of administration

-Intravenous; 1. Administration as primary anaesthetic agent with 100% oxygen.

2. Administration as an analgesic adjunct to nitrous oxide/oxygen

-Epidural administration

-Subarachnoid administration

Pharmacokinetics

It is described as a 3 compartment model with an average distribution time of 0.72 minutes.

Redistribution time of 13.7 minutes

Elimination half life 148 minutes.

Plasma protein binding is approximately 92.5% and 80% of the administered dose is excreted in 24 hrs.

The liver and intestine are the major sites of biotransformation

Sufentanil has immediate onset of action. A dose dependent attenuation of the sympathetic response to surgical stress has been demonstrated at i.v dose of 8-30 microgram/kg

Peak plasma concentration of sufentanil administered epidurally is reached within 10mins and is 46 times lower than those after i.v administration.

Pharmacodynamics

Cardiovascular system

Sufentanil has weak cholinergic activity hence should be used with caution in patients with cardiac arrhythmias

It produces bradycardia by binding to M3 receptors. It slows AV node conduction and prolongs PR interval

Opioids may induce hypotension especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Respiratory system

Respiratory depression is dose related and can be reversed by the

specific narcotic antagonist, Naloxone, but repeated dose of the antagonist may be necessary because the duration of respiratory depression may last longer than the opioid antagonist.

Marked respiratory depression accompanies profound analgesia.

It can persist in the post-operative period and if sufentanil has been given intravenously it can recur.

Hyperventilation during anaesthesia may alter the patient's response to CO₂ thus affecting respiration post-operatively.

The incidence and severity of early respiration with epidural administration may be less if adrenaline is added.

Musculo skeletal system

Induction of muscle rigidity, which may also involve the thoracic respiratory muscles, can occur but the risk may be reduced if intravenous injections are administered slowly.

Central nervous system

Sufentanil produces euphoria, sedation and miosis

Gastrointestinal tract

Sufentanil causes nausea, vomiting and biliary spasm

Adverse effects

Respiratory depression

Various studies have showed that respiratory depression may occur after any opioid, irrespective of its route of administration

Urinary retention

Sufentanil is likely to interact with opioid receptors located in sacral segments of spinal cord. This in turn promotes inhibition of sacral parasympathetic outflow which causes detrusor muscle relaxation and an increase in maximum bladder capacity leading to urinary retention.

Pruritus

Most common side effect is pruritis. The incidence is 0-100%. It may be generalized or localized to the face, neck and upper thorax.

Nausea and vomiting

Intraoperative incidence is 30%. It may be due to the cephalad migration of the drug and subsequent interaction with opioid receptors in vascularised Area postrema.

Hypotension

Intrathecal pethidine and sufentanil cause hypotension and the mechanism is not known.

This effect is mediated at the spinal level and hence neuraxial opioids are not an exemption from this effect.

Other effects

Chest wall rigidity

Apnoea

Diaphoresis

Emesis

Dizziness

Blurred vision

Allergic reactions and asystole have been reported

Over dosage and treatment

The over dosage of sufentanil manifest itself as an extension of its pharmacological actions.

Effects	Treatment
Hypoventilation	Oxygen therapy
Severe resp.depression	Naloxone
Hypotension	Parentral fluid therapy
Pruritus	Chlorpheneramine

Dosage

1. Administration as primary anaesthetic agent with 100%Oxygen

	Adult	Children
Initial dose	: 8-30mic/kg	10-25mic/kg
Maintenance dose	: 0.5-0.75mic/kg	0.5-0.75mic/kg

2. Administration as an analgesic adjunct to Nitrous oxide/Oxygen

Initial dose : 1-8mic/kg

Maintenance dose : 0.1-0.5mic/kg

3. Epidural administration for post .op. pain relief: 30-50mic
for 4-6 hrs

4. Labour analgesia (along with bupivacaine):15-30mic

5. Subarachnoid block: 2.5-10mic

Interactions

Barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non selective CNS depressants may potentiate the depressive effects of sufentanil

Mono-amine oxidase inhibitors must be discontinued 2 weeks prior to the administration of sufentanil.

OPIATE SYSTEM

“Among the remedies which it has pleased almighty god to give to man to relieve his sufferings, none is so universal and efficacious as opium”.

-Sydenham 1680.

The term opioid refers to all exogenous substances natural and synthetic that binds specifically to any of the several sub population of opioid receptors.

Opioid receptors: discovered by Pert and Snyder in 1974.

Types: Mu, Kappa, Sigma, Delta and Epsilon.

Distribution: Widespread areas in brainstem and spinal cord.

1. Areas associated with emotion – amygdala and limbic system
2. Area postrema
3. Along the course of pain pathways in medial thalamus
4. Spinal cord – marginal zone
 - substantia gelatinosa

RECEPTOR	EFFECT	AGONIST	ANTAGONIST
$\mu 1$	Supraspinal analgesia	Meptazinol β -endorphin	Naloxone, pentazocaine
$\mu 2$	Hyperventilation, Bradycardia, Physical dependence, Euphoria, Ileus	Morphine, Pethidine, Fentanyl, Sufentanil, Alfentanil	Nalbuphine
δ	Modulate μ activity	Leu-enkephalin	Naloxone, Metenkephalin
K	Analgesia Sedation Hypoventilation Miosis	Dynorphin Pentazocine Butorphanol Buprenorphine	Naloxone
Σ	Dysphoria Hypertonia Tachycardia Tachypnoea	Pentazocine Ketamine	Naloxone
ϵ	Stress induced alteration in nociception	B-endorphin	-

INTRATHECAL NARCOTICS

‘NARCOTIC’ means a drug, which produces sleep or stupor. Opiate receptors were identified in the central nervous system in 1973 and 1977. The endogenous Opioids were discovered by HUGHES et al in 1975 and TSANG et al in 1976. Opioid receptors in spinal cord was demonstrated by LA MOTTE et al in 1976. In the same year, YAKHSH and RUDY, demonstrated analgesia in animals produced by spinally applied opioids. Intrathecal opioid was first used in man by WANG et al in 1979. Extradural opioids was first used by BEHAR et al in 1979

Opioid receptors are present in great concentration in dorsal horn of spinal cord. There are three types of μ (mu) κ (kappa) δ (delta). Spinal opioids act mainly through μ receptors but kappa & delta also play a role. These drugs act by suppression of sensory input at REXED LAMINA II & V of the dorsal horn in the substantia gelatinosa of spinal cord. It is recognized that opioids suppress nociceptive input at the spinal level by their action on the opioid receptors in the spinal cord by bypassing the blood and blood brain barrier. Small doses of opioids administered into the subarachnoid space provide profound and prolonged segmental analgesia. Numerous studies have shown that spinal opioids can provide profound post operative analgesia with less central and systemic adverse effects than opioids

administered systemically.

Predicted advantages of intrathecal opioid

1. Segmental analgesia with no motor loss.
2. No autonomic block with consequent absence of hypotension.
3. Availability of larger number of drugs.
4. Existence of specific antagonist.

Factors affecting efficacy

Opioids differ in regard to their efficacy and side effect profile depending on whether they are hydrophilic or lipophilic.

HYDROPHILIC: Morphine

LIPOPHILIC: Alfentanil

Fentanyl

Sufentanil

Meperidine

Lipophilic opioids diffuse quickly into epidural fat and venous plexus. Their action is characterized by rapid onset and shorter duration of action. Hydrophilic drugs like morphine diffuse slowly into the tissues and have long latencies.

Uses of Intrathecal narcotics

Acute pain

1. Post operative pain
2. Post traumatic pain
3. Other acute pain conditions

E.g: pancreatitis

Chronic pain

1. Malignancy
2. Non malignant chronic pain

For operative procedures

Lower limb and lower abdominal surgeries

Side effects

1. Nausea and vomiting
2. Sedation
3. Itching
4. Urinary retention
5. Early or late respiratory depression

Less common side effects

1. Mental status changes
2. CNS excitation
3. Hyperalgesia
4. Herpes labialis virus reactivation
5. Neonatal morbidity
6. Sexual dysfunction
7. Cardiac dysarrhythmias
8. Anaphylaxis
9. Thermoregulatory dysfunction

DOSAGE OF INTRATHECAL OPIOIDS

DRUG	DOSE	DURATION(hrs)
Morphine	0.1-0.5mg	8-24
Meperidine	10-30mg	10-30
Diamorphine	0.05-0.1mg	20
Fentanyl	<50mcg	2
Sufentanil	<10mcg	2

FACTORS INCREASING THE RISK OF RESPIRATORY DEPRESSION

1. Repeated dose of opioids
2. IV sedative and concomitant use of narcotic and other respiratory depressants
3. Advanced age
4. Coexisting disease
5. Thoracic epidural placement
6. General anaesthesia
7. Increased intrathoracic pressure
8. Patient position

Combination of local anesthetic with opioids for spinal anaesthesia:

The rationale for the combination of local anesthetic with opioids is that these two type of drugs eliminate pain by acting at different sites, the local anesthetic at the nerve axon and the opioid at the receptors in the spinal cord. Newer developments include increasing use of local anesthetic and opioids particularly in obstetric population. Opioids have been frequently used in association with local anesthetic in regional anaesthesia in order to obtain faster onset, longer period of analgesia and superior quality of anaesthesia.

SPECIFIC NARCOTIC ANTAGONIST:

Naloxone 1-4 µg/Kg IV

SPREAD OF OPIOIDS IN THE CEREBROSPINAL FLUID

Opioids that are injected into the lumbar intrathecal space exert their analgesic effect by activation of spinal opioid receptors located in the substantia gelatinosa of the dorsal horn.

In addition, they can spread upward through the passive flow of cerebrospinal fluid to reach the vasomotor, respiratory and vomiting centers of the brain.

The rostral spread of intrathecal opioids is thought to be responsible for unwanted effects such as respiratory depression, hypotension, nausea and vomiting.

Systemic absorption and redistribution to the brain is an alternative route for activating brain-stem opioid receptors that may account for early side effects, whereas rostral spread within the cerebrospinal fluid may be responsible for late side effects.

HISTORY AND REVIEW OF LITERATURE

History of Subarachnoid block

In 1885, James Leonard Corning, a New York neurologist first used cocaine experimentally in dogs. In man, the first spinal anaesthesia was conducted by August Bier on 16th august 1898 with cocaine 3ml as 0.5% solution.

It was soon followed by Rudolf Matas in America and Tuffier in France.

Bupivacaine

Bupivacaine was synthesized in Sweden by Ekenstam and his colleagues in 1957 and was first used clinically by L.J. Tervio in 1963.

Intrathecal Opioids

Gate control theory of pain (1965) by Melzack and Wall focused the attention on importance of dorsal horn of spinal cord in the modulation of pain.

In 1973, Pert and Snyder identified the specific opiate receptors in the substantia gelatinosa of dorsal horn of spinal cord.

In 1976, spinal effects of intrathecal opiates in animals were demonstrated by Yaksh and Rudy

In 1977, Wang, Naurs and Thomas studied the effects of intrathecal

morphine in men with intractable pain of lower limb due to malignancy invading the lumbosacral plexus.

In 1980, Davier et al, identified that respiratory depression with intrathecal morphine could be reversed with low dose naloxone, without reversing the analgesia.

In 1981, Yaksh and Rudy described the action of intrathecal pethidine and morphine in primates by iontophoretic administration of the drugs into the substantia gelatinosa. They found out high level of opiate binding in substantia gelatinosa indicating the presynaptic action of opiate. Spinal opiates also seemed to cause significant elevation of nociceptive threshold.

In 1988, Inagaki Y, Takeyama E studied the efficacy of post operative pain relief after the use of intrathecal buprenorphine with local anesthetic agent and found it to prolong the post operative analgesia.

Spinal opioids and labour analgesia

Opiates have been used as analgesic agents in obstetrics since the Babylonians discovered their pain relieving properties.

Subarachnoid block was first used for obstetric delivery in 1901 by Kreis in Germany

Articles quoting the use of Intrathecal pethidine in labour and delivery

were reported in British Journal of anaesthesia in 1987.

Morphine was the first opioid to be used intrathecally but has the limitations of long latency, high incidence of maternal side effects, poor perineal analgesia and delayed respiratory depression. (Alper M, intrathecal morphine; a new method of obstetric analgesia, *Anesthesiology*, 1979: 51; 378-379).

Sufentanil and intrathecal anaesthesia

The increased availability of lipid soluble opioids with shorter latency and demonstration of synergistic effects of opioids when combined with local anaesthetic have led to the widespread use of neuraxial opioids in labour.

The effect of lipophilic agents are better when administered at the level at which analgesia is required. Commonly used opioids are meperidine, fentanyl and sufentanil. (Honet JE, Arkoosh VA, Norris MC et al. Comparison among intrathecal fentanyl, meperidine and sufentanil for labour analgesia. *Anaesthesia Analgesia* 1992;75:734-739)

Justins et al 1982: the dose of local anesthetic required for labour pain relief can be diminished to one half to one third with the addition of intrathecal opioids and provides excellent analgesia for the entirety of labour.

Dahlgren, Gunnar et al 1997: compared the effects of intrathecal sufentanil 2.5 and 5 µg, fentanyl 10µg, and placebo when administered together with hyperbaric bupivacaine 0.5%, 12.5mg for caesarean section. They demonstrated that small doses of fentanyl or sufentanil (synthetic opioids) added to bupivacaine (local anesthetic) for spinal anesthesia for caesarean section reduced the need for intraoperative antiemetic medication and increased the duration of analgesia in the early post operative period compared with placebo.

Michael J. Cousins and Lawrence E. Motler, intrathecal and epidural administration of opioids, *Anaesthesiology*, 1992; 61 : 276-310.

Robert K. Stoelting, *Pharmacology and Physiology in Anaesthetic practice*, 3rd edition.

Thomas E.J. Healy ; Wylie and Churchill Davidson's, *A practice of anaesthesia* 7th edition; 1995

LE BARS et al in 1976, and JURN and HEINZ in 1979 demonstrated that in electrophysiological terms , it is “C” and “A delta” fiber's primary afferent input to wide dynamic range cells in spinal cord which appear to be most sensitive to the intrathecally applied morphine. The selectivity may be due to inhibition of temporal facilitation.

In 1977, WANG, NAUSS and THOMAS studied the effect of intrathecal morphine in man in intractable pain of back and leg due to malignancy, invading lumbosacral plexus. Predictable relief of pain was achieved without motor or sensory block.

In 1980, DAVIES et al, identified respiratory depression after intrathecal morphine, reversed with systemic Naloxone, without reversing analgesia in 3 out of 6 patients.

In July 1998, NGIAM SK, CHONG JL compared the effects of intrathecal fentanyl 15 mcg added to 7.5 mg of bupivacaine, 10 mcg of sufentanil added to 7.5 mg of bupivacaine and 7.5 mg of bupivacaine alone in 60 ASA I&II patients coming for elective cesarean section. They found that the duration of effective analgesia of bupivacaine alone was prolonged with the addition of sufentanil and fentanyl by 358% and 256% respectively. None of the patients required additional intraoperative analgesia.

In 1999, KENNETH H. GWIRTZ M.D, JERRY V. YOUNG M.D et al belonging to Indiana University School of Medicine, Indianapolis, Indiana studied the safety and efficacy of intrathecal opioid analgesia for acute postoperative pain.

In June 1999, R. FOURNIER, M.D., E. VAN GESSEL, M.D., A. WEBER M.D., Z. GAMULIN M.D., compared the effects

of intrathecally administered sufentanil 7.5mcg and fentanyl 40mcg for postoperative pain relief after total hip replacement. They concluded that both the groups had rapid and profound pain relief with comparable onset and duration of action.

MATERIALS AND METHODS

After getting the approval from the ethical committee of the Department of Anesthesiology, Government Rajaji Hospital attached to Madurai Medical College, Madurai, the study was conducted in 80 patients undergoing elective and emergency caesarean section after getting consent and explaining the procedure details to the patients.

Exclusion criteria

Term parturients aged 18 to 35 years classified under ASA physical status I and II, I_E and II_E who were termed fit for subarachnoid block were selected. Patients with coexisting medical diseases were excluded. Patients who were converted to general anaesthesia were excluded later.

Preoperative preparation

After preoperative assessment, the pregnant patients were premedicated with

Inj. Metaclopramide 10mg

Inj. Ranitidine 50mg – intramuscularly 45 minutes before
induction of anaesthesia

Patients were randomly allotted into two groups.

GROUP I: Inj bupivacaine (0.5%) heavy 1.5cc + 0.1cc of
normal saline

GROUP II: Inj bupivacaine (0.5%) heavy 1.5cc +sufentanil
5µg

Procedure details

In the preoperative visit, patients were explained of the procedure details.

Then baseline preoperative pulse rate and blood pressure were recorded. Intravenous life line was started with 18G cannula.

All patients were preloaded with 15-20ml/Kg of normal saline/ ringer lactate.

Following emergency drugs and equipments were kept ready before anaesthetic intervention.

1. Boyle's apparatus
2. Continuous flow - oxygen source
3. Laryngoscope with all size blades
4. Airway – all sizes
5. Suction apparatus

6. Drugs – ephedrine, dopamine, atropine, adrenaline

7. Naloxone

Patients were put in lateral position and with strict aseptic precautions lumbar puncture was done with Quincke Babcock's standard spinal needle – 23 G.

After ensuring free flow of cerebrospinal fluid, the drug was injected as per the group assigned.

The assigned amount of sufentanil and normal saline were taken in sterile tuberculin syringe.

After injection patient was put up in supine position with left lateral tilt and 100% oxygen given through Magill's breathing circuit until delivery of the baby.

Recording of data

Time of subarachnoid injection.

Hemodynamics

Blood pressure, pulse rate, respiratory rate were monitored every 2 minutes for first 10 minutes and every 5 minutes till end of surgery.

Time of starting of the surgery

Any discomfort during visceral handling was noted

Hypotension is said to have occurred if there was 20% fall from baseline blood pressure. The treatment includes 100% oxygen, intravenous fluids and ephedrine in incremental dose.

Bradycardia

It was treated with inj. Atropine 0.6mg intravenously.

Nausea and vomiting

It was treated with inj. Metaclopramide 10mg intravenously.

Pruritus

It was treated with diphenhydramine 25mg intravenously.

Two segment regression time

Time taken to decrease from maximal initial sensory level by two segments from the initial level is noted.

Sedation score

Brain and Ready's sedation score was employed

1. Fully awake
2. Drowsy
3. sleeping but arousable
4. arousable to painful stimulus
5. Not able to awake

Foetal outcome

After delivery, fetal outcome was assessed with Apgar score calculated at 1 minute and 5 minutes. Reflexes like sucking, rooting and moro's were tested and recorded.

Total duration of analgesia

In the post operative period total duration of analgesia was taken as that period from the time of induction (subarachnoid block) till patient's first requirement for analgesic medication.

Pain was evaluated using linear Visual Analogue Scale (VAS).

VAS 0- no pain

10- Worst pain

If VAS score was more than 6, supplementary analgesia was given and the study concluded.

Also in the post operative period every mother and baby were

followed up for any complication like respiratory depression, postoperative nausea and vomiting, pruritus, urinary retention and hypotension.

Statistical significance was brought out by Student's t – test.

OBSERVATION AND RESULTS

In this randomized single blinded study, conducted in 80 patients, the subjects were allocated into 2 groups

GROUP I: Inj bupivacaine (0.5%) heavy 1.5cc + 0.1cc of normal saline

GROUP II: Inj bupivacaine (0.5%) heavy 1.5cc +sufentanil 5µg.

DEMOGRAPHIC DATA

Both groups were comparable in age, height and duration and nature of surgery

Age

<i>AGE (IN YEARS)</i>	<i>GROUP I</i>	<i>GROUP II</i>
MINIMUM	20	20
MAXIMUM	34	42
MEAN	24.97	25.825
STANDARD DEVIATION	3.133	5.032

There was no statistically significant variation in age of the patients in both the groups.

Both the groups were comparable.

Height

<i>HEIGHT (IN CENTIMETERS)</i>	<i>GROUP I</i>	<i>GROUP II</i>
MINIMUM	133	136
MAXIMUM	160	162
MEAN	151.22	153.67
STANDARD DEVIATION	5.90	5.91

There was no statistically significant variation in height of the patients in both the groups.

Both the groups were comparable.

Maximal level of sensory blockade

SENSORY LEVEL	GROUP I	GROUP II
T2	-	7
T3	-	1
T4	10	22
T5	1	1
T6	22	9
T7	1	-
T8	5	-
T9	-	-
T10	2	-

Maximal sensory level achieved for pin prick sensation T6 in Group I and T4 in Group II

Highest level of blockade achieved was T4 in Group I&T2 in Group II.

Lowest level of blockade achieved was T10 in Group I and T6 in Group II.

A significant variation noted in maximal level of sensory blockade in both the groups.

Two segment regression time

<i>TWO SEGMENT REGRESSION TIME (MINUTES)</i>	<i>GROUP I</i>	GROUP II
MINIMUM	30	45
MAXIMUM	65	90
MEAN	44.75	64.25
STANDARD DEVIATION	10.12	13.51

Two segment regression time duration of analgesia as measured by two segment regression time were 44.75min in Group I with standard deviation of 10.12, 64.25min in group II with standard deviation of 13.51.

A significant variation noted in two segment regression time in both the groups.

Total duration of analgesia

Total duration of analgesia was 76.5 minutes in group I with standard deviation of 19.12 (Around one hour and fifteen minutes)

150.37 minutes in group II with a standard deviation of 25.5, (Around two hour and thirty minutes).

Complications

SIDE EFFECTS	GROUP I	GROUP II
HYPOTENSION	2	7
NAUSEA & VOMITING	-	6
RESPIRATORY DEPRESSION	-	-
PRURITUS	-	16
BRADYCARDIA	-	2
URINARY RETENTION	-	-
DISCOMFORT	21	-
SEDATION	-	2

Hemodynamic variable

With regard to blood pressure, a fall in blood pressure more than 20% from the baseline value was considered hypotension.

In Group I, 5% of patients had hypotension.

In Group II, 17, 5 % of patients had hypotension.

The hypotension in the study group required either intravenous fluids or injection ephedrine and oxygen supplementation.

None of them required any further intervention.

With regard to pulse rate, a fall in pulse rate below 60 per minute was considered bradycardia.

About 5% of patients had bradycardia in Group II and it was treated with inj. Atropine 0.6 mg intravenously. None of them required any further intervention.

No bradycardia noted in Group I patients.

Sedation

Intraoperative sedation was excellent in Group II patients.

In Group II

47.5 %of patients had sedation score of 2.

2.5% of patients had sedation score of 3.

In Group I

All patients had sedation score of 1.

Nausea and vomiting

In Group II

15% of patients had nausea and vomiting.

Eventually all responded to Inj.metaclopramide 10mg intravenously.

In group I

No patients had nausea or vomiting.

Pruritus

In Group II

40% of patients had pruritus.

All responded to inj. Diphenhydramine.

In group I

No patient had pruritus

Respiratory depression and urinary retention

No respiratory depression and urinary retention was noted in both the groups.

Intraoperative discomfort

In group II 100% of the patients were comfortable.

In group I 52.5% of the patients had intraoperative discomfort.

We had to necessarily manage them with analgesics and intravenous anaesthetics.

Fetal outcome

Apgar was calculated at 1 minute and 5 minutes after deliver of baby. There was no neonatal respiratory depression noted. Apgar score was comparable in both the group.

It did not show statistically significant variation among the two groups.

The score was 6.9 ± 0.659 at the 1st minute and 8.725 ± 0.75 at the 5th minute in the sufentanil group.

The score was 7.22 ± 0.65 at the 1st minute and 8.95 ± 0.75 at the 5th minute in the control group.

None of the babies had any further neurological complications.

DISCUSSION

80 patients undergoing caesarean section with the physical status of ASA I, II, I_E & II_E were taken up for the study. They were randomly allocated into two groups, 40 patients in each group. Variables like age, height were standardized in both groups.

Group I (control group) received 1.5 cc of 0.5% bupivacaine with 0.1 ml of normal saline intrathecally.

Group II (study group) received 1.5 cc of 0.5 % bupivacaine with 5 µg of sufentanil intrathecally.

Anaesthetic variables

Intra-operative study

In this study a lower dose of bupivacaine is used. We used 1.5ml of hyperbaric bupivacaine with 0.1 ml (5 µg) of sufentanil making a total volume of 1.6 ml to assess the quality of anaesthesia.

The quality of intra operative surgical anaesthesia was excellent in (100 %) of patients in sufentanil group as compared to 47.5 % in control group. All the patients who received 1.5ml of hyperbaric bupivacaine with sufentanil were comfortable during the intra operative period.

About 52.5% of the patients who received bupivacaine alone had intraoperative discomfort significantly. They had to be necessarily maintained with adjuvant analgesic or intravenous anaesthetics

Addition of opioids aid in relieving the discomfort that could be caused by visceral handling. This is well brought out in other studies done by Peach. M.J. et al in 1994 & M.S. Batra et al.

Total duration of analgesia

The total duration of analgesia evaluated was significantly prolonged in sufentanil group; 150.38 ± 25.5 minutes compared to 76.5 ± 19.12 minutes in control group

The requirement for the first dose of analgesia was significantly prolonged in sufentanil group.

**This value was statistically significant as calculated by student's t-test.
($p < 0.001$)**

The results of our study goes in consistent with the study by Braga Ade F, Braga F.S. et al at School of Medical Sciences, Campinas, Sao Paulo, Brazil. (Eur.J. Anaesthesiol. 2003 Aug; 20(8): 631-5)

2-segment regression time

2-segment regression of anesthesia took longer; 64.25 ± 13.52 min in sufentanil group as compared with 44.75 ± 10.12 in control group. This was proved statistically significant.

**This value was statistically significant as calculated by student's t-test.
($p < 0.001$)**

Hemodynamic variables

The incidence of hypotension was about 17.5% in the study group compared with 5% in control group.

The hemodynamics after 5 minutes was 93.5 ± 16.41 mm of Hg in sufentanil as compared with 101.75 ± 18.5 in control group.

Opioids produce nausea and vomiting by direct stimulation of chemoreceptor trigger zone. This effect is dose related and can be treated with anticholinergic or phenothiazines, those are antagonistic at dopamine receptor. Route of opioid administration does not influence the occurrence of vomiting.

The incidence of vomiting in our study is 15%.

Pruritus

This is a common side effect especially with obstetric population. Incidence from previous studies showed result of 0-100%.

This effect is dose dependent as shown by GilMcmorland, 1990, (personal communication), this effect is centrally mediated due to cephalad migration of the opioid to brain stem and fourth ventricle

It is self limiting, can also be antagonized by anti-histamines. .No patients required treatment in our study.

40% of patients in our study had pruritus, which was dose related.

Consistent with the study conducted by Braga Ade et al concluded pruritus was the most common side effect and had the significantly higher incidence when a dose of sufentanil 7.5mic was used(Eur J Anaesthesiol.2003 Aug;20(8):631-5)

Sedation

Intra operative sedation was excellent in sufentanil group.

In Control Group patients required sedative supplementation whereas no sedation was required in the sufentanil group.

About 47.5 % had sedation score of 2& 2.5% had sedation score of 3.

Fetal outcome

Apgar was calculated at 1 minute and 5 minutes after deliver of baby. There was no neonatal respiratory depression noted. Apgar score was comparable in both the group.

It did not show statistically significant variation among the two groups.

The score was 6.9 ± 0.659 at the 1st minute and 8.725 ± 0.75 at the 5th minute in the sufentanil group.

The score was 7.22 ± 0.65 at the 1st minute and 8.95 ± 0.75 at the 5th minute in the control group.

None of the babies had any further neurological complications.

So far varied numbers of studies have been conducted showing the efficacy of sufentanil in providing comfortable intraoperative period and prolonged post operative pain relief with minimal complication.

This study delineates that the acceptable dose range without much morbidity in hospitals with moderate post operative care and without high dependency unit with 5 µg of sufentanil Intrathecally.

It has been found out by this study that 5µg of Intrathecal sufentanil with 1.5ml of 0.5% hyperbaric bupivacaine provides

An improved quality of intraoperative surgical anesthesia.

Increase in the duration of two segment regressions (64.25 ± 13.51).

Increase in the total duration of analgesia (150.375 ± 25.50).

The occurrence and intensity of side effects were so minimal and not significant. The benefit associated with administration of intrathecal sufentanil in a dose of $5\mu\text{g}$ outweighs the disadvantages of it.

CONCLUSION

It has been found out by this study that addition of 5µg of sufentanil to low dose (7.5mg) of 0.5% of bupivacaine intrathecally in caesarean section provides improved quality of surgical anaesthesia and analgesia without significantly increasing maternal and fetal side effects than using bupivacaine alone.

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PROFORMA

Case no.			Study / control	Date
Name :	Age/sex:	I.P. NO:	Ht:	Wt:
Unit:		ASA:		
Patient pre operative condition			Vital signs	
Blood investigation:			Pulse rate:	
Hb %:			BP:	
Blood sugar:			CVS:	
Sr. creatinine			RS:	
Premedication : inj. Ranitidine 50mg			Time of injection	
Inj. i.m Metaclopramide 10mg i.m				

PARAMETERS STUDIED

1. Time of intrathecal injection
2. Highest level of sensory block achieved (pinprick)
3. Intraoperative discomfort – yes / no
4. Level of block at the end of surgery
5. Two segment regression time
6. Duration of post operative analgesia
7. VAS

0 Hr	1Hr	2 Hr	3 Hr	4 Hr	5 Hr

8. APGAR

Sign	Score		
	0	1 minute	5 minutes
Heart rate	Absent	<100/ min	>100/min
Respiratory effort	Absent	Slow, irregular	Good, crying
Color	Blue, pale	Body pink, extremities blue	Completely pink
Reflex irritability (response to insertion of nasal catheter)	Absent	Grimace	Cough, sneeze
Muscle tone	Limp	Some flexion of extremities	Active motion

- | | |
|--|------------|
| 9. Hypotension (.30% fall from base line BP) | - yes / no |
| 10. bradycardia (<60/min) | - yes / no |
| 11. incomplete sensory block | - yes / no |
| 12. pruritus | - yes / no |
| 13. nausea & vomiting | - yes / no |
| 14. any complications for the baby | - yes / no |

Intra operative monitoring

time	Sensory level	PR	BP	Sedation score	Remarks

Sedation score

1. Fully awake
2. Drowsy
3. sleeping but arousable
4. arousable to painful stimulus
5. Not able to awake

VAS

- 0-1 excellent
- 2-4 good
- 5-6 fair
- 7-8 poor
- 9-10 no pain relief

